

A Prospective, Randomized Comparison of the Postoperative Administration of Tramadol and Morphine following Primary Total Knee Arthroplasty

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Abstract

Background: Different techniques and medications are used to achieve pain relief and early mobilization after total knee arthroplasty (TKA). However, the relationship between subacute postoperative pain and early functional recovery remains to be fully resolved. We examined the effects of low-dose tramadol, and morphine on subacute postoperative pain management with NSAID in patients after TKA.

Hypothesis: The low-dose tramadol combined with NSAIDs are effective for subacute postoperative pain in TKA.

Methods: We prospectively studied 81 patients who underwent primary TKA. Before surgery, we randomly assigned participating patients into one of three treatment groups; Group NSAID, Group Tramadol, or Group Morphine. The postoperative pain intensity was measured and recorded by physical therapists with a visual analogue scale (VAS) at rest (rVAS) and during movement (mVAS) on the day before surgery, and on postoperative days (PODs) 3, 7 and 14. The lower leg functional recovery was also evaluated by the range of motion (ROM) of the knee, and the quadriceps muscle strength (% muscle strength).

Results: Twenty-two patients from each group completed the study. The mean rVAS scores of the groups showed no significant differences between throughout the postoperative period. The mean mVAS scores showed no differences on PODs 7, 10, and 14. However, the mVAS scores of Group Tramadol were significantly lower than those of Group NSAID on POD 3 ($p=0.0216$). No significant differences were found among the groups in ROM or % muscle strength. The incidence of constipation in Group Morphine was significantly higher than that in Group NSAID ($p=0.0026$).

Conclusion: Tramadol 100mg/day was effective for postoperative pain management, especially in the first week after TKA.

Level of Evidence: Level II, low-powered prospective randomized trial.

Keywords: Total knee arthroplasty (TKA); Tramadol; Morphine; Postoperative pain

Introduction

The management of pain in the immediate postoperative period is one of the most critical aspects in orthopedic surgery including Total Knee Arthroplasty (TKA). Different techniques and medications are used to achieve good pain relief and early mobilization after TKA. At present, the analgesic modalities include epidural analgesia, intravenous opioids, patient-controlled analgesia (PCA), peripheral nerve block and local intra-articular or periarticular analgesic injection [1-4]. Many studies about periarticular injection have reported that it achieves good results, reducing acute post-operative pain within 72

hours and increasing patient satisfaction [2,3,5,6]. However, the control of pain following TKA remains imperfect, especially in relation to "subacute" postoperative pain management.

Tramadol is primarily used to treat mild to severe pain, in both the acute and chronic stages. Tramadol has been prescribed for postoperative pain in various fields. Mishra et al. [7] compared the efficacy of single-dose oral ketorolac (20 mg) to tramadol (200 mg) administered preoperatively and postoperatively for dental extraction pain, and found that tramadol was equally effective to ketorolac for relieving pain. Several orthopedic studies also showed the efficacy of intraarticular or intravenous tramadol in relieving postoperative pain [8-11]. Thus, we hypothesized that oral tramadol would be effective for managing the subacute postoperative pain after TKA.

In the present study, we examined the effects of low-dose tramadol, and morphine on subacute postoperative pain management with NSAID in patients undergoing TKA. We also evaluated the lower leg functional recovery and adverse events including nausea, vomiting and constipation in three groups.

Patients and Methods

Participants

We prospectively studied 81 consecutive patients who underwent primary total knee arthroplasty (TKA) in our university hospital between April 2015 and September 2016. All operations were performed by two certified knee surgeons. The research ethics committees in Gifu University School of Medicine approved all of the study procedures. All patients provided their written, informed consent for participation in the present study. The subjects who were offered enrollment included adults (age: 24–90 years) who were scheduled for primary TKA via a parapatellar approach, as described the previous work [12,13]. The exclusion criteria included bilateral TKA, the presence of allergy or sensitivity or contraindications to tramadol or morphine, neuromuscular disease, dementia, major organ disease, pregnancy, a history of substance or alcohol abuse, and opioid tolerance or dependence. Fifteen patients were excluded from this study (Figure 1).

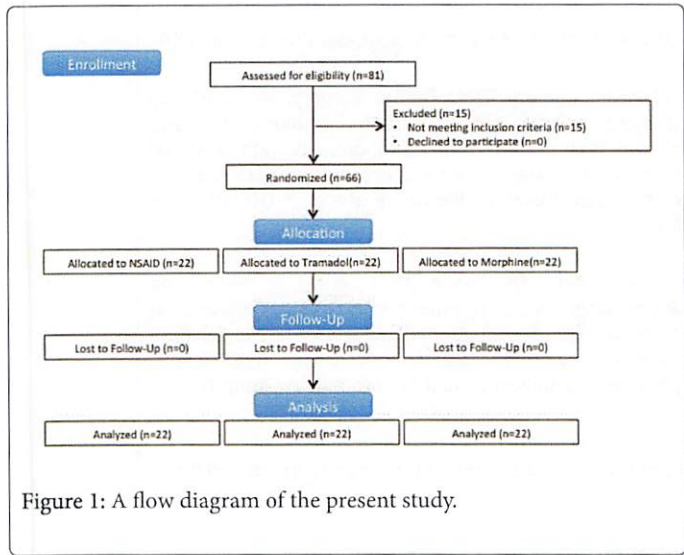


Figure 1: A flow diagram of the present study.

Perioperative procedures

At one hour and thirty minutes before their arrival at the operating room (OR), all patients were orally premedicated with clonidine (3 µg/kg) and ranitidine (150 mg). After their arrival at the OR, standard monitoring and peripheral venous access was obtained. General anesthesia was induced with thiopental (4 mg/kg), remifentanyl (0.5 µg/kg/min), and rocuronium (0.6 mg/kg). Following tracheal intubation, anesthesia was maintained with sevoflurane (1.2~1.5%) and remifentanyl (0.2-0.4 µg/kg/min).

Patients received intraarticular injections of 40 mL of solution, including 10 mL of 1.0% ropivacaine, 1,000 mg tranexamic acid, and additional normal saline during suturing. Using a 50-mL syringe, the solution was injected into the medial/lateral/posterior joint capsule

and the periosteum and around the incision site of the joint capsule after the fixation of the implants.

Ultrasound (US)-guided femoral nerve block (FNB) was performed immediately after surgery using 10 mL of 0.375% ropivacaine. The correct level of analgesia was confirmed by monitoring the disappearance of the electrical signal after stimulation, with an intensity of 5 mA shortly after injection and by assessing the integumentary sensation in the dermatome of the femoral nerve by pinprick tests.

All patients received intravenous postoperative analgesia for 48 hours with a continuous infusion of fentanyl (50 µg/h). They received oral celecoxib 400mg once followed by an additional 200 mg on postoperative day 1.

Randomization

Before surgery, we randomly assigned participating patients into one of the three treatment groups; Group NSAID, Group Tramadol, or Group Morphine. Patients in Group NSAID received celecoxib (200 mg) every 12 hours from postoperative day 2 until postoperative day 14. Patients in Group Tramadol received tramadol (25 mg) every 6 hours from postoperative day 2 until postoperative day 14 and also received celecoxib as same as Group NSAID. Patients in Group Morphine received morphine (5 mg) every 8 hours from postoperative day 2 until postoperative day 14 and also received celecoxib as same as Group NSAID. In addition, we administered rescue NSAIDs as necessary in each of the groups (Table 1).

Patients with postoperative pain were rescued by diclofenac sodium suppository 25 mg or loxoprofen 60 mg. The number of times of rescue drugs for pain was recorded for 14 postoperative days. Furthermore, we defined within 48 hours after operation as an acute postoperative period, and examined the number of times of rescue drugs in each group.

	Group NSAID	Group Tramadol	Group Morphine
Preoperative	Randomly assigned participating patients into one of three treatment programs		
Operation Day	Intraarticular injections of 40 mL of solution, including 10 mL of 1.0% ropivacaine, 1,000 mg tranexamic acid, femoral nerve block (FNB) 10 mL of 0.375% ropivacaine and Fentanyl IV 50 µg/h		
POD 1	Fentanyl IV 50 µg/h and, Celecoxib 400 mg once followed by an additional 200 mg		
POD 2	Celecoxib 400 mg/day	Celecoxib 400 mg/day + Tramadol 100 mg/day	Celecoxib 400 mg/day + Morphine 15 mg/day
3	↓	↓	↓
4	↓	↓	↓
5	↓	↓	↓
6	↓	↓	↓
7	↓	↓	↓
8	↓	↓	↓
9	↓	↓	↓

10	↓	↓	↓
11	↓	↓	↓
12	↓	↓	↓
13	↓	↓	↓
14	↓	↓	↓

Table 1: Postoperative pain management protocol after TKA.

Outcome measurements

The postoperative pain intensity was measured and recorded by the physical therapists (who were not aware of the treatment group) using a 100-mm visual analogue scale (VAS) (where 0=no pain, and 100=the worst pain imaginable) at rest (rVAS) and during movement (mVAS) until postoperative day 14. They also evaluated the lower leg functional recovery by the range of motion of the knee and quadriceps muscle strength.

To measure the manual muscle force, the muscle tester (Isoforce, OG GIKEN, Japan), the same method as MMT, was used on the day before surgery, and postoperative days 3, 7 and 14 (Table 1). The preoperative muscle strength was considered to be 100%, and the ratio of the postoperative muscle strength to the preoperative muscle strength was calculated.

Adverse events

Adverse events, including constipation, nausea, vomiting, drowsiness, dizziness, confusion, fatigue, itchiness, and headache were examined. Patients with postoperative constipation were treated with sennosides (24 mg) or magnesium oxide (500 mg), as necessary. Patients with postoperative nausea and vomiting were treated with metoclopramide (10 mg) or prochlorperazine maleate (5 mg), as necessary. The numbers of times that rescue drugs were administered for constipation, nausea, and pain were recorded until postoperative day 14.

Statistical methods

A power analysis (two-tailed α error, 5%; β error, 20%) was performed before the study. The calculation of the required sample size was based on the quadriceps strength, which was measured during inpatient rehabilitation following unilateral total knee arthroplasty with controlled-release oxycodone in a previous study (13.7 ± 6.2 lb) and with a placebo (8.8 ± 4.0 lb) [7].

Nineteen patients per group were required in order to reveal a statistically significant difference between each group. Pearson's chi-squared test and Bonferroni correction were used to compare the number of patients who showed adverse events among the 3 groups. The Prism 5.0 software program was used to perform the statistical analysis. P values of <0.05 were considered to indicate statistical significance. The data were presented as the mean $\pm$ SD.

Results

The demographic and clinical data and postoperative pain

The age ($p=0.92$), BMI ($p=0.70$), operative time ($p=0.062$) and intraoperative blood loss ($p=0.19$) did not differ to a statistically significant extent (Table 2).

Variables	NSAID	Tramadol	Morphine	p value
N	22	22	22	22
Age (y)	73.2 $\pm$ 7.3	72.6 $\pm$ 14.5	73.9 $\pm$ 7.3	P=0.92
Weight (kg)	59.8 $\pm$ 12.5	61.2 $\pm$ 18.8	64.5 $\pm$ 8.4	P=0.54
Height (cm)	150.4 $\pm$ 7.8	153.1 $\pm$ 10.1	154.7 $\pm$ 7.9	P=0.25
Body Mass Index (kg/cm ²)	26.3 $\pm$ 4.3	26.0 $\pm$ 5.0	27.1 $\pm$ 4.5	P=0.70
Sex, M/F	4 / 18	3 / 19	6 / 16	-
Side of Surgery (R/L)	12 / 10	9 / 13	15 / 7	-
Surgery Time (min)	108.9 $\pm$ 14.8	122.0 $\pm$ 23.2	122.9 $\pm$ 25.2	P=0.062
Intraoperative Blood Loss (ml)	43.2 $\pm$ 23.5	76.5 $\pm$ 116.5	42.1 $\pm$ 30.5	P=0.19
Diagnosis (OA/RA)	21 / 1	21 / 1	22 / 0	-

Table 2: Baseline patient characteristics and preoperative, intraoperative data.

No significant differences were found among the groups in the preoperative NSAIDs intake, VAS scores at rest and during movement. The postoperative pain intensity was measured with a 100-mm rVAS and mVAS. There were no significant differences in the mean rVAS scores of the groups throughout the postoperative period until postoperative day 14 (Figure 2A). There were no significant differences in the mean mVAS scores on postoperative days 7, 10, and 14.

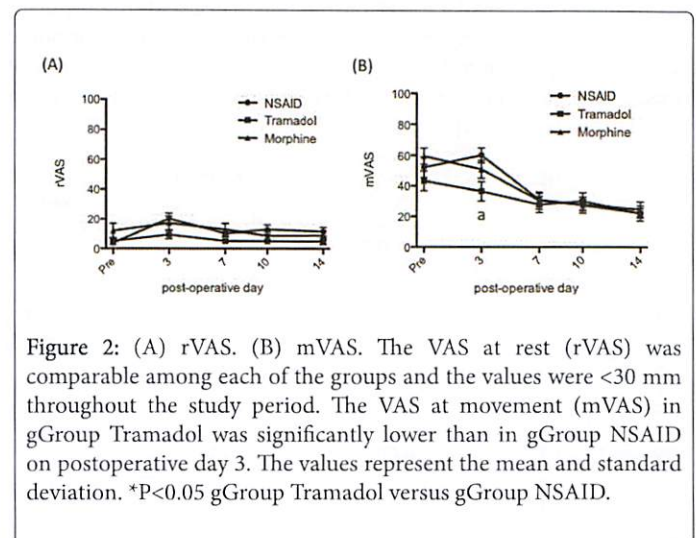


Figure 2: (A) rVAS. (B) mVAS. The VAS at rest (rVAS) was comparable among each of the groups and the values were <30 mm throughout the study period. The VAS at movement (mVAS) in gGroup Tramadol was significantly lower than in gGroup NSAID on postoperative day 3. The values represent the mean and standard deviation. *P<0.05 gGroup Tramadol versus gGroup NSAID.

($p=0.0216$) (Figure 2B). These results suggest that tramadol was effective, especially for early postoperative pain during movement. The number of times for NSAID rescue dose in acute postoperative period was not significantly differences in each group (0.14 ± 0.47 in Group NSAID, 0.05 ± 0.21 in Group Tramadol, 0.14 ± 0.35 in Group Morphine). The number of times for NSAID rescue dose after postoperative day 2 was not significantly differences in each group, either (1.86 ± 3.97 in Group NSAID, 0.72 ± 1.78 in Group Tramadol, 0.73 ± 1.28 in Group Morphine).

Postoperative functional recovery

The lower leg functional recovery was evaluated according to the range of motion (ROM) and muscle strength using a muscle tester. The preoperative active range of motion did not differ among the groups to a statistically significant extent. The ROM did not differ among the groups throughout the postoperative period (Figure 3A). Furthermore, the % muscle strength did not differ among the groups to a statistically significant extent (Figure 3B).

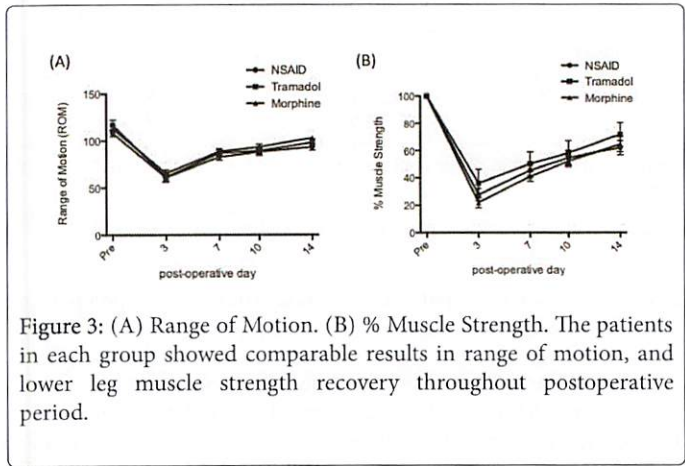


Figure 3: (A) Range of Motion. (B) % Muscle Strength. The patients in each group showed comparable results in range of motion, and lower leg muscle strength recovery throughout postoperative period.

Adverse events

The rates of constipation were as follows: Group NSAID, $n=4$ (18.2%), Group Tramadol, $n=11$ (50.0%), and Group Morphine, $n=15$ (68.2%). The rate of constipation in Group Morphine was significantly higher in comparison to Group NSAID ($p<0.001$); however, the rate of constipation in Group Tramadol was comparable to that in Group NSAID and Group Morphine (Table 3).

	NSAID (%)	N=22	Tramadol (%)	N=22	Morphine (%)	N=22	P value
Constipation	4 (18.2)		11 (50.0)		15 (68.2)*		0.0026
Nausea	0 (0)		4 (18.2)		5 (22.7)		0.068
Vomiting	0 (0)		0 (0)		0 (0)		-
Drowsiness	0 (0)		0 (0)		0 (0)		-
Dizziness	0 (0)		0 (0)		0 (0)		-
Confusion	0 (0)		0 (0)		0 (0)		-
Fatigue	0 (0)		0 (0)		0 (0)		-
Itchiness	0 (0)		0 (0)		0 (0)		-

Headache	0 (0)	0 (0)	0 (0)	-
*P<0.05: Group morphine vs. Group NSAID in Bonferroni correction				

Table 3: Postoperative side effects, presented as number and percentage.

Nausea occurred frequently in Group Tramadol ($n=4$, 18.2%), and Group Morphine ($n=5$, 22.7%) compared with Group NSAID. The incidence of nausea did not differ to a statistically significant extent (Table 3). The number of times that constipation rescue drugs were used was significantly higher in Group Morphine than in Group NSAID (3.1 vs 0.2 , $p=0.0005$). The number of times that nausea rescue drugs were used did not differ to a statistically significant extent among the groups (0.00 in Group NSAID, 0.77 in Group Tramadol, and 0.91 in Group Morphine). None of the patients reported drowsiness, dizziness, confusion, fatigue, itchiness, or headache during the postoperative period until postoperative day 14 (Table 3). Furthermore, any renal insufficiency due to tramadol or NSAID use was not seen in the cohort of patients.

Discussion

This study examined the effects of adding tramadol, and morphine to NSAID in comparison to NSAID alone in patients who underwent TKA, with a particular focus on subacute postoperative pain management. We found that the addition of low-dose tramadol was effective for postoperative pain management, especially within the first week after surgery.

Tramadol, a weak opioid agonist (selective μ receptor) that acts on the central nervous system, is an inhibitor of the neuronal reuptake of noradrenalin and enhances the release of serotonin [14]. Tramadol has been used for treating postoperative pain in the various fields. In the field of orthopedic surgery, few studies have investigated the analgesic effects of the intraarticular administration of tramadol after knee arthroscopic surgery [8-10]. Furthermore, Yilmaz et al. [11] reported that intravenous tramadol (1.5 mg/kg) was more effective than intravenous paracetamol (1 g) for treating postoperative pain after lumbar disc surgery. These orthopedic studies also showed the efficacy of intraarticular or intravenous tramadol in relieving postoperative pain. However, they focused on the acute pain experienced in the early postoperative period.. To date, the control of subacute pain following TKA remains imperfect. Thus, one of the strong points in this study is that we focused on the control of subacute pain following TKA.

Recently, Mochizuki et al. reported that the combination of tramadol and acetaminophen (TRAM/APAP) has been shown to be feasible for subacute postoperative pain management after TKA [15]. They concluded that group TRAM/APAP was shown to be superior to that of NSAID for postoperative pain reduction and the number of days required for walking after TKA. Thus, tramadol seems to be effective for relieving postoperative pain.

In the present study, we examined the efficacy of low-dose tramadol in combination with NSAID for fourteen days after surgery in comparison to morphine. Reducing complications, including vomiting, and nausea, is an important aspect of postoperative pain management. According to the background information of the patients, the average physical status was relatively small. Furthermore, we had already performed a preliminary investigation using tramadol (200 mg/day), but found that it was associated with an increased rate of

complications, including constipation and nausea. Thus, we decided to use low-dose tramadol (100 mg/day). The dose of morphine (15 mg) was equivalent to 100 mg of tramadol. Opioids, including morphine, are known to be effective drugs for managing postoperative pain. However, side effects are frequently observed, including nausea, and constipation. In addition, reducing opioid dosage with multimodal analgesia is recommended for prevention of severe postoperative complication such as respiratory depression [16]. Thus far, as much as low-dose opioids could be preferred for postoperative pain management, there have been no comparative studies with opioids alone for postoperative management after TKA. In this study, adverse events-including constipation and nausea-were most frequently observed in Group Morphine, even with a 15 mg dose.

The management of pain in the immediate postoperative period is one of the most critical aspects in allowing earlier rehabilitation [17]. In the previous work of Matsumoto et al. [18] examined the efficacy of the transdermal fentanyl patch in the muscle strength recovery after TKA, and the patients treated by the transdermal fentanyl patch showed early muscle strength recovery. In this study, they also examined the recovery of ROM or % muscle strength in each group. However, tramadol or morphine was not associated with the significant recovery of the ROM or % muscle strength in comparison to NSAID. We cannot simply compare the results of the present study and the previous work of transdermal fentanyl patch studies [18], because the perioperative analgesic procedures were different, including the use of epidural analgesia and the type of NSAID. However, the transdermal fentanyl patch might be superior to low-dose tramadol for postoperative pain management and % muscle recovery. Thus, a direct comparative study of the effects of the transdermal fentanyl patch and a comparable dose of tramadol could yield interesting results.

The most common adverse effects of tramadol include nausea, dizziness, dry mouth, indigestion, abdominal pain, vertigo, vomiting, constipation, drowsiness and headache [7,14,19]. In comparison to other opioids, respiratory depression and constipation are considered to be less of a problem with tramadol [4]. In fact, constipation was more common in patients who used morphine in comparison to those who used NSAID and tramadol, and the use of constipation rescue drugs was significantly higher in the morphine group. Tramadol was not associated with significant differences in constipation or constipation rescue drug use. However, half of the patients in the tramadol group experienced constipation. Thus, for even better postoperative pain management, an increased dosage of tramadol may be needed and tramadol should always be combined with an appropriate laxative for the treatment of opioid-induced constipation.

Conflict of Interest

None

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